Immune correlates of protection against HIV infection and how to elicit them

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To the Editor: Immune correlates of protection against HIV infection are an important topic of investigation in HIV research as the analysis of such correlates could help the design of novel vaccinal and prevention approaches to the disease (reviewed in ref. 1) The definition of mucosal correlates of protection, in particular, is of extreme importance given that the vast majority of HIV infections are sexually transmitted. Veazey presents data of experiments in the animal model in which interferon beta (IFNβ) was applied topically in the genital site. Not surprisingly, IFNβ resulted in mucosal immune activation, but, unexpectedly, animals were protected from SHIV infection.[2]

We analyzed mucosal immune correlates of protection in highly exposed HIV

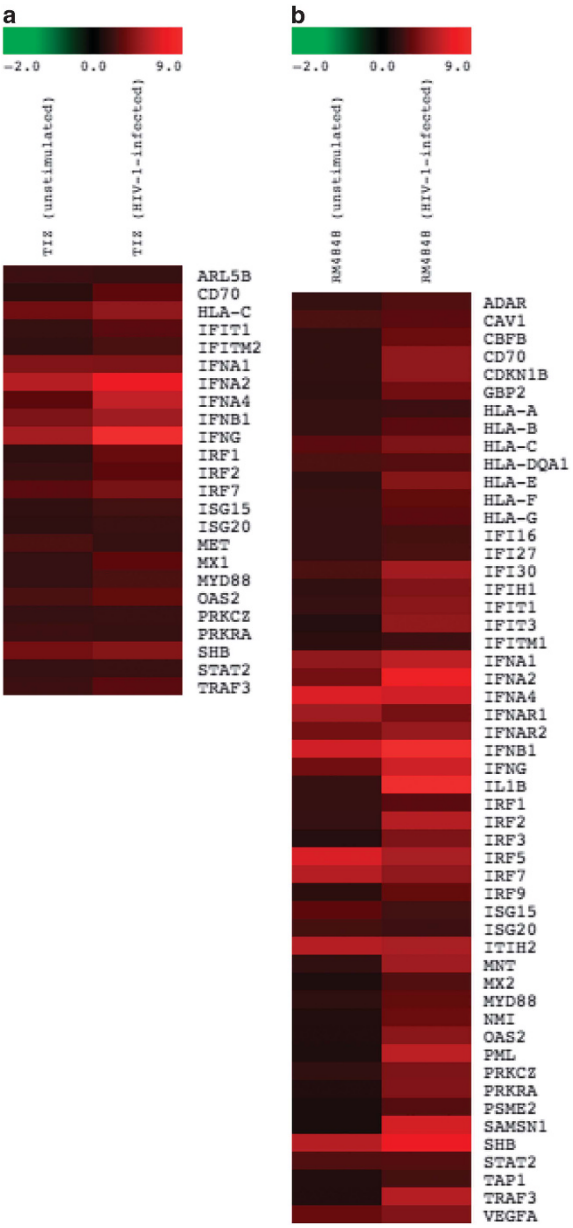

Figure 1 Messenger RNA (mRNA) expression of genes that are part of the type I interferon (IFN) signal transduction pathway in peripheral blood mononuclear cells (PBMC) that were cultured in medium containing two different thiazolides: tizoxanide (TIZ) or RM-4848, and were or were not *in vitro* infected with HIV (the R5 tropic HIV-1BaL strain was used in the experiments shown herein). mRNA expression was assessed by real-time quantitative polymerase chain reaction, calculated relative to five housekeeping genes and shown as fold-change expression from the untreated sample. Gene expression (*n*-fold) is shown as a color scale from green to red (−2 to +9) (MEV multiple experiment viewer software); only genes that are upregulated are shown. (**a**) PBMC cultured in medium containing TIZ (10 μg/ml) that were either uninfected or HIV1-infected. Results at day 7 post infection are shown. (**b**) PBMC cultured in medium containing RM-4848 (10 μg/ml) that were either uninfected or HIV1-infected. Results at day 7 post infection are shown.

seronegative (HESN) women and were surprised to realize that protection against HIV infection was indeed associated with immune activation. Thus, in HESN women, a significant increase of proinflammatory cytokines, chemokines, and chemokine receptors was detected.[3,4] These results led to the hypothesis that immune activation in itself is not sufficient to favor HIV infection, but rather could result in protection, possibly because more potent local immune responses could more efficiently contain exposure to (limited) amounts of HIV. The finding by Veazey that interferon-stimulated genes (ISG) are upregulated as well in this animal model adds an extremely interesting level of complexity, as many of the proteins produced by such genes (e.g., APOBEC, TRIM, IFITs, etc) are endowed with strong antiviral properties.

Upregulation of IRG within a milieu of immune activation could thus be a plausible way to explain mucosal resistance to HIV infection, but how would it be possible to stimulate these mechanisms in ways that are less cumbersome than repeated topical INFβ applications? We recently analyzed the possible immunomodulatory effects of thiazolides (TZD), a class of oral agents characterized by broad anti-infective activities, and observed that these compounds potently stimulate innate immunity and upregulate the type 1 IFN pathway. *In vitro* analyses of these compounds in HIV infection showed that TZD drastically inhibited *in vitro* HIV-1 replication (>90%) as a result of the activation of innate immune responses and the upregulation of several ISG[5] (**Figure 1**). As TZD are currently approved in the United States for the treatment of different pathogens,[6] and as they are less toxic, less expensive, and much simpler to use than topical IFNβ, it would be important to verify whether TZD might represents a clinically practicable strategy to achieve protection against HIV acquisition.

AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript; MB and DT performed the experiments summarized in **Figure 1**.

DISCLOSURE

Prof J-F Rossignol is a board member of Romark Laboratories, L.C. The remaining authors declared no conflict of interest.

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